A CLINICAL PATHOLOGIC STUDY OF MERCURIALENTIS MEDICAMENTOSUS*

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MERCURIALENTIS WAS FIRST BROUGHT TO OUR ATTENTION BY DR WALTER ATKINSON in 1942.[1] At the annual meeting of this Society, he reported the slit lamp observation of a "brownish colored reflex" on the anterior capsule of the lens in 36 of 70 persons who were working with mercury in the manufacture of thermometers. In a subsequent presentation,[2] he reported the histochemical and spectrographic identification of mercury in the lenses of a patient who had had chronic mercurialism and who had mercury pigmentation of the lenses. This type of pigmentation has since been reported as a result of exposure to mercury in a variety of industries. In addition to thermometer workers,[1,2,3,4] it has been found amongst direct-current meter repairers,[5,6] in the felt hat industry,[1,7] and in workers exposed to the mercury-zinc amalgams of batteries.[8] In recent years, improved working conditions with proper ventilation of industrial plants and enforcement of other hygienic measures, has reduced the incidence of exposure to and systemic effects of inorganic mercurials.

The first report of mercury pigmentation of the anterior lens capsule secondary to topical medication, was that of Abrams[9] in 1963. He observed mercurialentis in more than 70 patients who had glaucoma and who had been treated with miotics containing phenyl-mercuric nitrate (PMN) for more than three years.

In 1971 and in 1974, before this Society, Kennedy[10,11] reported the development of band keratopathy in patients after prolonged use of pilocarpine solutions containing the preservative, PMN. He also noted that the topical use of eye drops containing PMN significantly increased the

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concentration of mercury within the eye and often led to deposits of pigment in the cornea and the lens. In a recent communication,* he stated that he had observed some 40 patients with mercurialentis, and all had used miotics with PMN as the preservative.

We wish to report the deposition of a pigment on the anterior capsule of the lens in 31 patients who had used a number of topical medications, each containing a mercurial preservative. In addition to the clinical observations of these patients, light and electron microscopic studies as well as electron probe analyses were performed on one lens and on an eye removed at autopsy. Another lens was examined by the techniques of X-ray fluorescence and neutron activation analysis.

CLINICAL OBSERVATIONS

Since 1965, 31 patients have been noted to have pigmentation of varying color and intensity in the pupillary portion of the anterior capsule of the lens (Fig. 1). Two patients were found to have a distinct golden coloration of the peripheral portion of Descemet's membrane, when viewed at the slit lamp with direct illumination. In others, this finding was less apparent or absent. The pigmentation of the lens was observed as early as three years after the commencement of the topical medication in two patients, and as late as 15 years in another. In 18 of the 31, the pigmentation was noted within six years after commencing the eye drops. Gonioscopically, the angle in several of these patients was noted to be lightly or darkly pigmented, generally more intense at the lower angle, but it was not possible to differentiate this pigment from melanin. In one patient, in addition to the lenticular pigmentation, there was progressive bilateral band keratopathy.

Twenty-nine of the 31 patients were under treatment for glaucoma and were using commercially available pilocarpine hydrochloride solution containing the preservative, PMN, in a dilution of 1:75,000. These drops were generally used four times a day. Twelve of the patients with glaucoma also used epinephryl borate drops once or twice daily. These contained the preservative, phenyl-mercuric acetate (PMA) in the dilution of 1:50,000.

Two of the 31 patients had chronic blepharitis and conjunctivitis and were using the antibacterial solution, sulfisoxazole diolamine, in which the preservative, PMN, was present in a dilution of 1:100,000. One of the patients admitted using it two to four times daily for more than four years,

*Letter, May 19, 1975

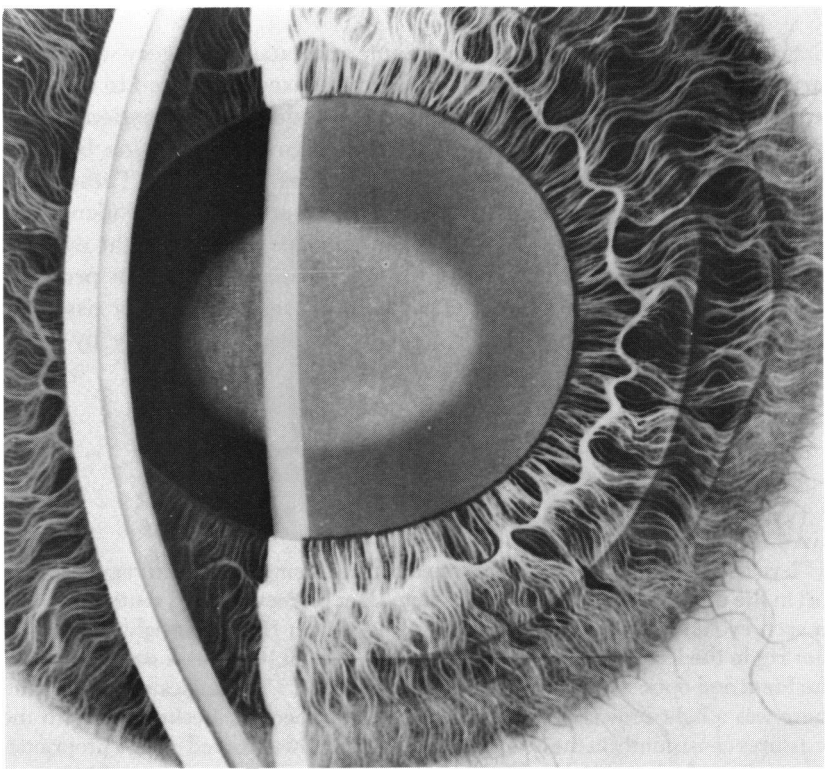

FIGURE 1
Artist's drawing illustrating pigmentation anterior lens capsule with pupil dilated.

and the other, the wife of a pharmacist, stated that she had been using these drops at least twice daily for twelve years. The pigmentation seen in these two patients were identical to that seen in the patients with glaucoma.

The pigmentation of the lens is readily seen at the slit lamp, especially when the pupil is partially dilated. In the early stages of the deposition, the color is lusterless gray or light yellow; later, yellowish brown, and finally, when the mercurial deposit is well established, it is brown to reddish brown. With the pupil dilated, the pigmentation is noted to fade off irregularly at the edges and there is no apparent deposition on the capsule in the areas covered by the iris when the pupil is miotic. The pigmentation appears to be innocuous as it does not seem to be associated with visual impairment.

LABORATORY STUDIES

Cataracts developed in 5 of the 31 patients and cataract surgery was necessary. The histologic findings of one of these lenses, as related to the mercury deposition will be discussed (Case 1). In addition, one patient whose lenses remained clear except for moderate pigment deposition but who died of ovarian carcinomatosis, willed her eyes for study. These were obtained for histologic examination by light and electron microscopy (Case 2). The cataractous lens (Case 1) and this patient's right eye and lens (Case 2) were also subjected to study with the electron probe to identify the character of the deposits in the lenses and in other tissues of the eye. The left lens of Case 2 was also subjected to study by X-ray fluorescence and neutron activation analysis.

CASE REPORTS

CASE 1

A 71-year-old white woman was examined in 1959, complaining of a vague discomfort in the eyes and periodic visual blurring. Her corrected visual acuity was 20/20 in each eye and the intraocular pressure was 31 mm Hg in the right eye and 27 mm Hg in the left eye. The visual fields were normal, the lenses were clear, and the fundi and optic discs were normal in appearance. The angles were open and there was a light brownish pigmentation of the trabecular meshwork. With the pressures consistently in the 30 mm range, treatment was started using a proprietary preparation of pilocarpine hydrochloride containing the preservative, PMN, in a dilution of 1:75,000. Using this medication four times daily, she had relief of the symptoms and a consistent reduction of the intraocular pressure below the 20 mm level.

In 1967, a dull light brownish pigmentation of the anterior capsule of the lens was noted in the miotic pupil. With the pupils dilated, the pigmented area of the capsule contrasted strikingly with the surrounding unpigmented capsule. At the edges of the colored area there was irregular fading of intensity.

In 1969, early, senile, cuneiform, opacities of the lenses were noted bilaterally and the visual acuity was at the 20/40 level in each eye. By October 1974, the pigmentation of the lens capsules was more intense with a coppery or reddish-brown tone. The cataract in the right eye had progressed further and the visual acuity had dropped to less than 20/100. At surgery, in order to avoid contact with the pigmented area, a fine cryoextractor tip was applied to the anterior capsule of the lens near the equator in the 12 o'clock meridian after the iris was retracted, and an intracapsular cataract extraction was done. The lens was immediately fixed in a solution of 5% gluteraldehyde. Small sections of the lens capsule and underlying cortex from different areas of the lens were imbedded in Araldite 502 and sectioned for light and electron microscopy.

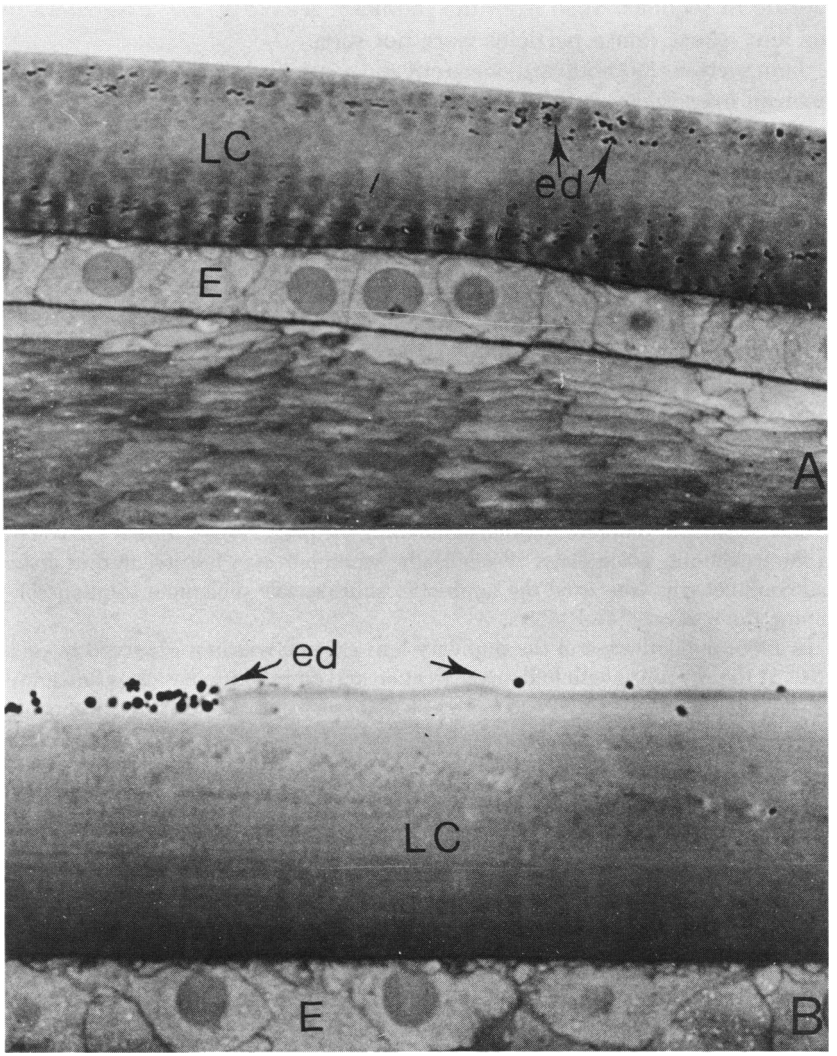

FIGURE 2

A: Light microscopic section through lens capsule (LC), with numerous dense particles (ed), and subcapsular epithelium (E) (×775). B: Light micrograph showing dense particles (ed) on lens capsule (LC) (×835).

MICROSCOPIC FINDINGS

Thick sections (1μ) were stained with basic fuchsin and methylene blue and examined with the light microscope. Dense black particulate matter, oval and rounded, of varying size were found on the surface and within the

capsule in sections taken from the pupillary area (Fig. 2). Elsewhere in the lens, these dense particles were not seen.

Thin sections (600-800 mμ) were cut and examined with the transmission electron microscope.* Again, in the pupillary area, as with light microscopy, dense particulate material was seen attached to the surface of the capsule and within the capsule itself (Fig. 3). Smaller particles, ranging down to the size of dust were seen throughout the full thickness of the capsule, and in addition, dense particles were found in the cytoplasm of some subcapsular epithelia. These did not appear to be membrane-bound.

CASE 2

A 41-year-old white woman was examined in 1956, and was found to have glaucoma. The intraocular pressure in each eye was elevated above the 30 mm Hg level. The discs were cupped and the visual fields showed bilateral early Bjerrum defects. The corrected visual acuity was 20/20 each eye. Gonioscopically, the angles were open, and there was light brownish pigmentation of the trabecular area. She was placed on pilocarpine hydrochloride drops (containing PMN) four times daily. In 1962, epinephryl borate solution (containing the preservative, PMA) was added to the treatment, twice daily. Periodically, when her eyes felt irritated or if she had conjunctivitis, she used the antibiotic, sulfisoxazole diolamine solution containing the preservative PMN.

In 1966, pigmentation of the pupillary lens capsule was first observed in each eye. At the slit lamp, with high magnification and direct illumination, a fine granular brownish pigmentation was noted on the lens capsule. During succeeding years, the intensity of the brownish deposit became more marked and was easily recognized even with a flashlight.

In December 1974, the patient was told that she had wide-spread metastasis from adenocarcinoma of the ovary. She stated that she wished to will her eyes for histologic study.

The patient died in a distant city on May 16, 1975, at 2:30 a.m. The eyes were enucleated at 4:00 a.m., but were not fixed until after 10:00 a.m. The right eye was fixed in 10% gluteraldehyde and the left eye was fixed in 10% formaldehyde solution. The eyes arrived at our laboratories on May 19, 1975. Because of the passage of more than 7 hours from the time of death to the beginning of fixation, the tissues showed considerable postmortem autolysis. The right eye was processed for histologic study by light and electron microscopy.

MICROSCOPIC FINDINGS

Dense particulate matter in varying concentrations was found in the corneal epithelium and stroma, in the trabecular meshwork, on and in the lens capsule and in the subcapsular epithelium and in the zonular fibers.

With light microscopy, the corneal deposits were located within the cytoplasm of epithelial cells and in some of the superficial stromal cells

*Siemens Elmiskope, Model #1A

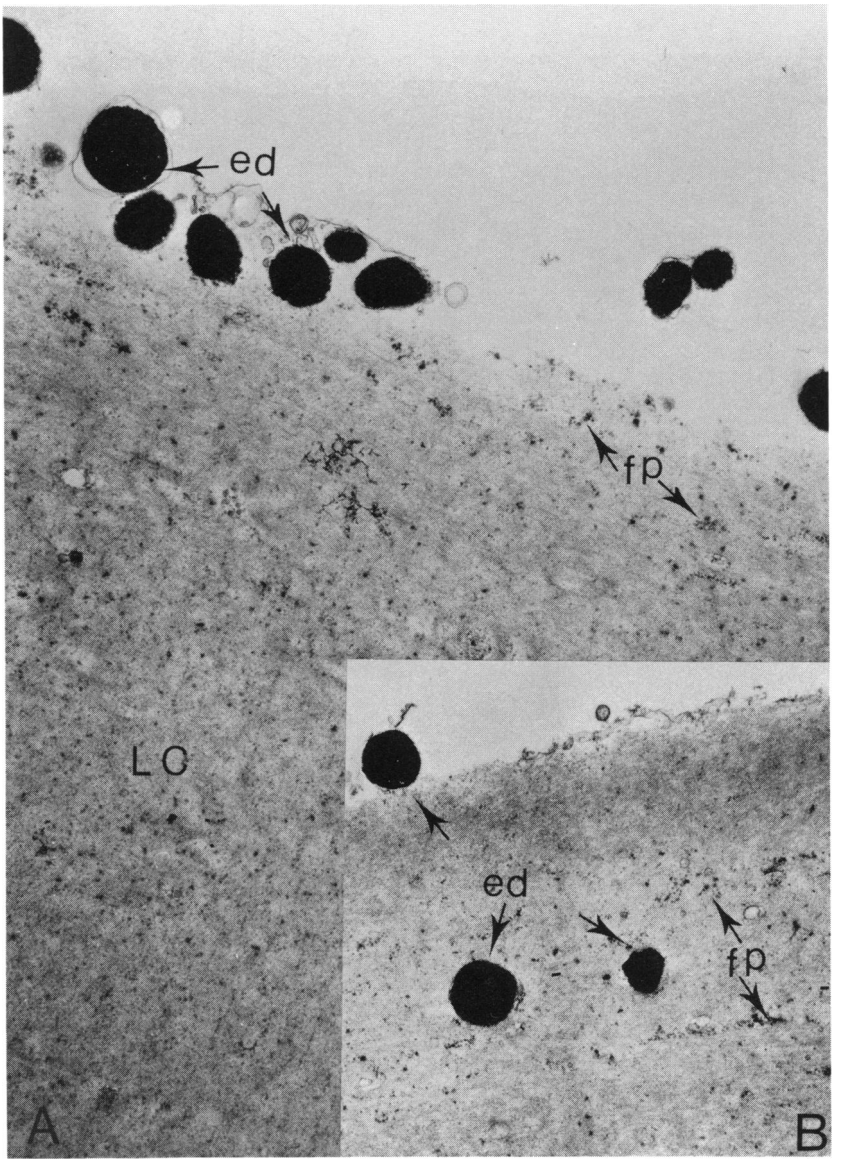

FIGURE 3

A: Electron micrograph showing electron dense particles (ed) on surface of lens capsule (LC), and fine dust-like particles (fp) throughout capsule (×9395). B: Electron dense particles (ed) on and in capsule, and finer deposits in capsule (fp) (×8005).

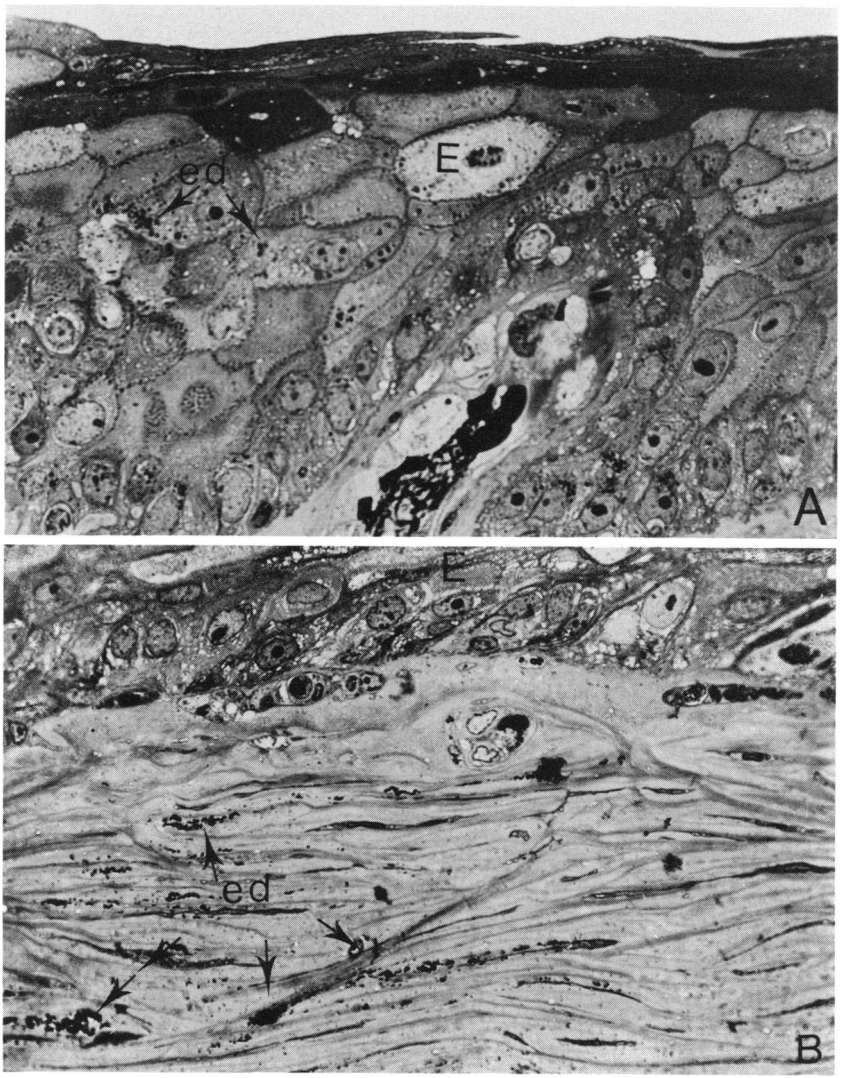

FIGURE 4
A: Light microscopic section of corneal epithelium (E), with dense particles in cytoplasm (ed) (×755). B: Superficial corneal stroma with fine deposits (ed) in stromal cells (×433).

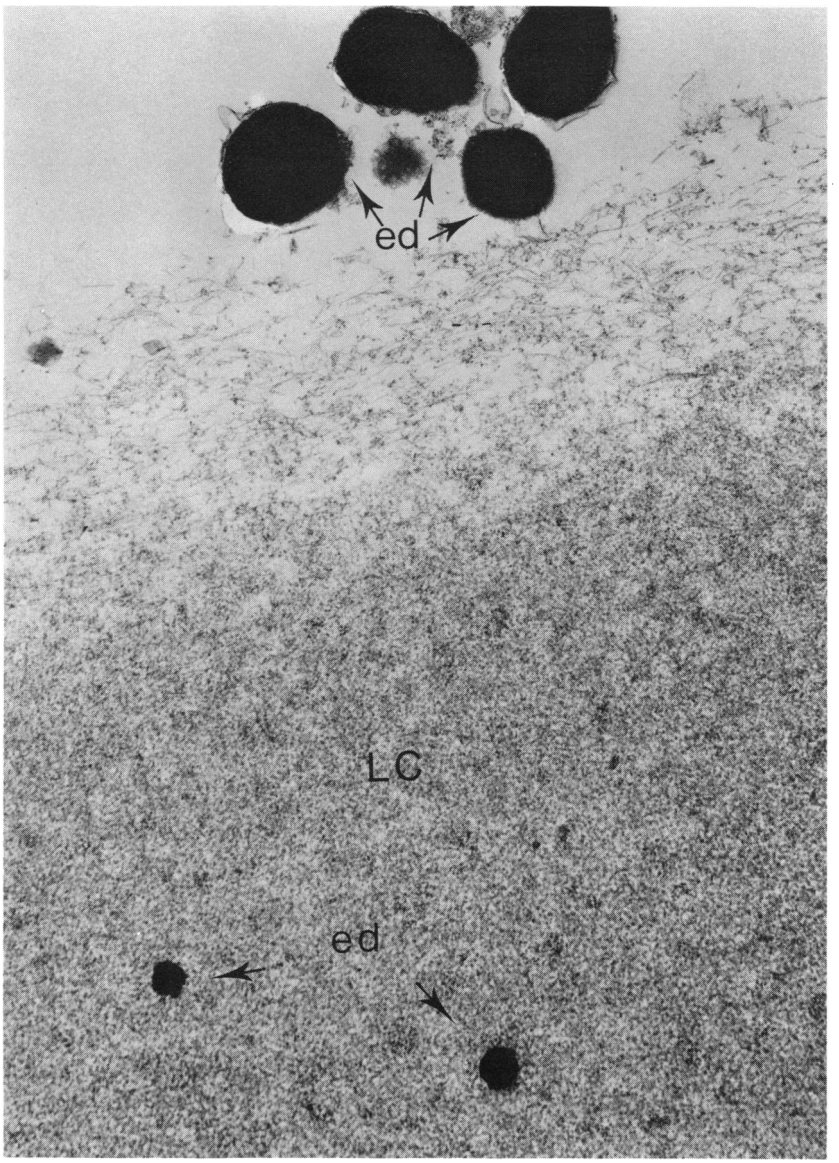

FIGURE 5
Electron micrograph, Case 2, with electron dense particles (ed) on and in lens capsule (LC) (×15,010).

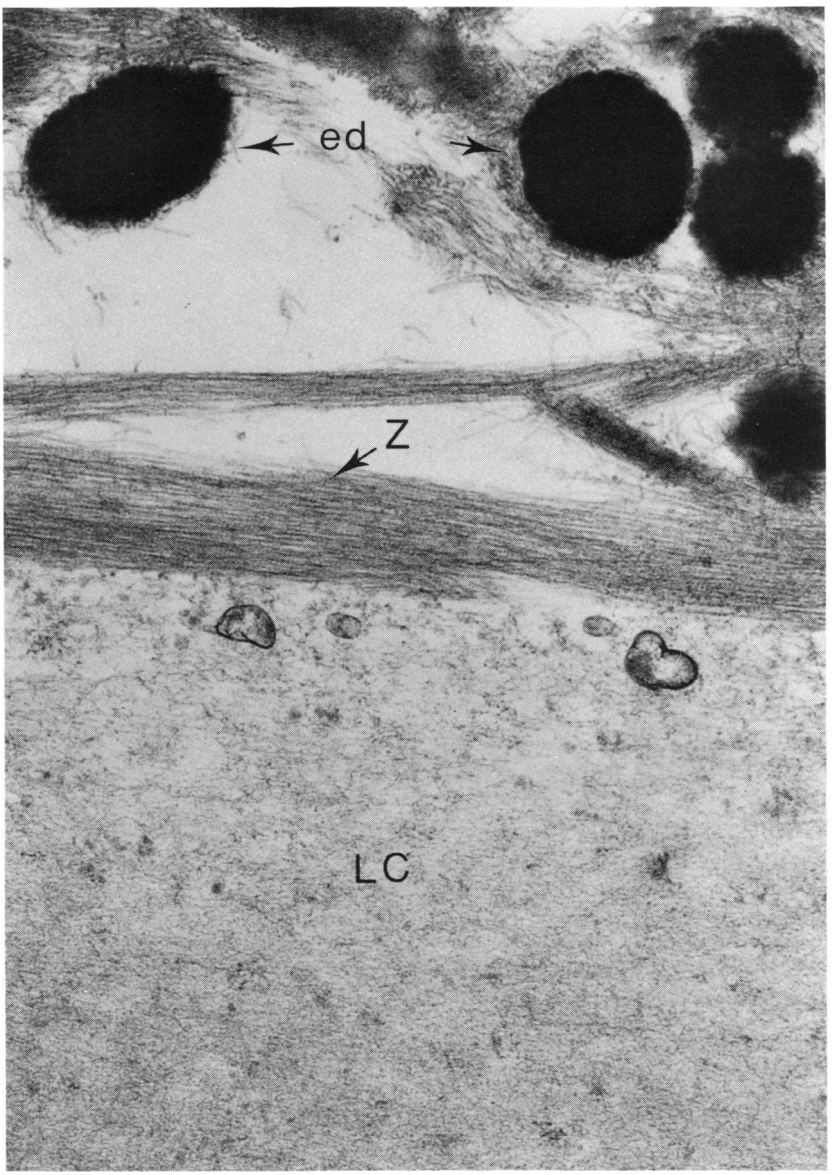

FIGURE 6
Electron micrograph, Case 2, showing electron dense particles (ed), in the zonular fibers (Z) at capsule periphery (×22,295).

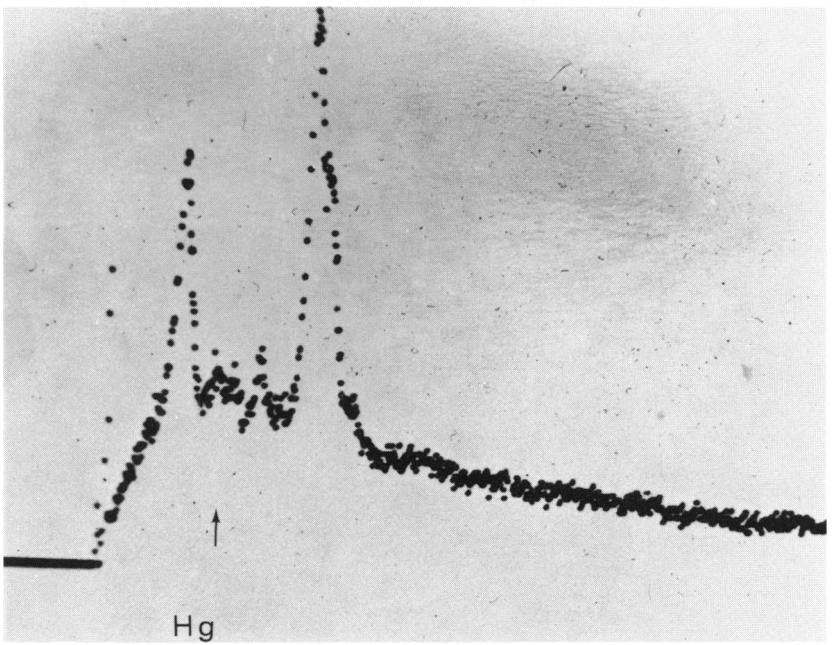

FIGURE 7
Analysis spectrum of electron microprobe study showing a small peak in the curve for mercury (Hg) (Case 1).

(Fig. 4). The material did not appear to be carried by phagocytes. The electron microscopic sections confirmed the epithelial deposits. The peripheral portions of Descemet's membrane and the corneal endothelium were studied and a few fine electron dense deposits were found in Descemet's membrane.

In the pupillary area, the lens capsule and the subcapsular epithelium showed deposits identical to those seen in Case 1 (Fig. 5). The dust-like deposits within the capsule were likewise seen. Between the zonular fibers, near their attachments to the lens capsule, were many electron dense particles similar to those seen on the lens capsule (Fig. 6).

Thick sections (1 to 2 μ) of the lens capsule near the pupil in Case 1 and in Case 2 (right lens), were prepared for scanning electron microscopy and electron microprobe analysis in an attempt to identify and localize metallic mercury or mercury in compounds. A minimal response for the presence of mercury was obtained as observed on the analysis spectrum in each case (Figs. 7 and 8).

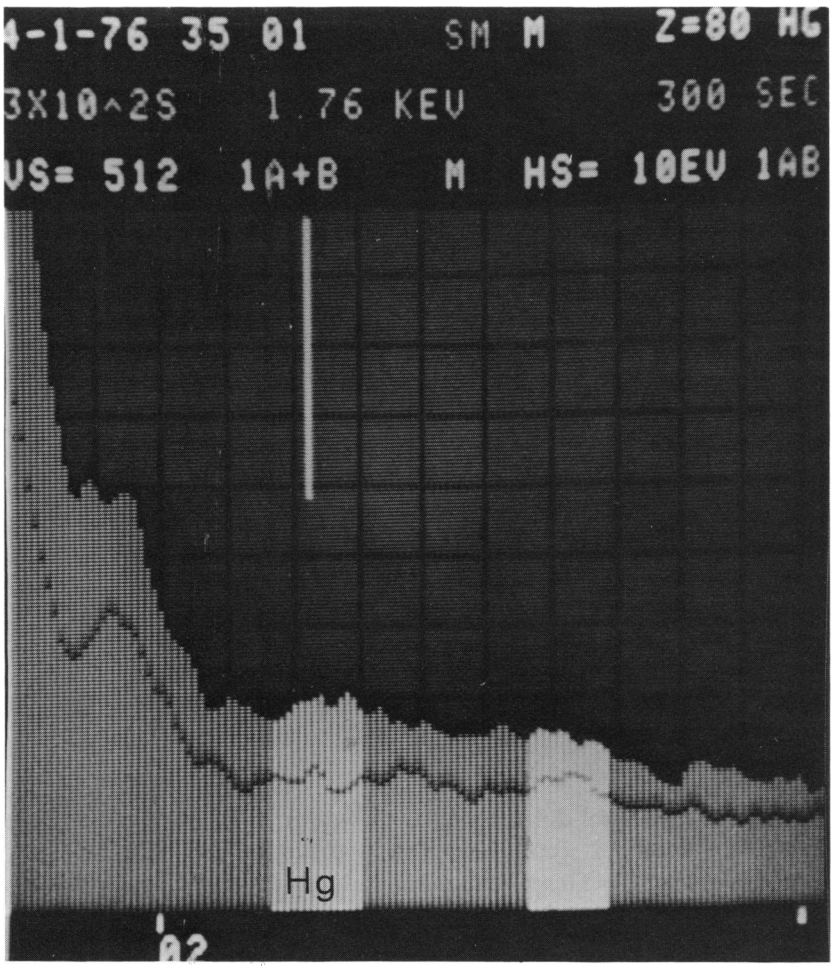

FIGURE 8
Analysis spectrum for mercury (Hg) with the scanning electron microscope and electron microprobe (Case 2).

The whole lens of the left eye of Case 2 was prepared by "critical point drying" and analysed by X-ray fluorescence. This technique, which attempts to determine the amount of mercury in the whole lens, produced questionable results with the mercury peak only slightly above the level of the background.

The left lens of Case 2 was also studied by the technique of neutron activation analysis. This is currently the most sensitive method for de-

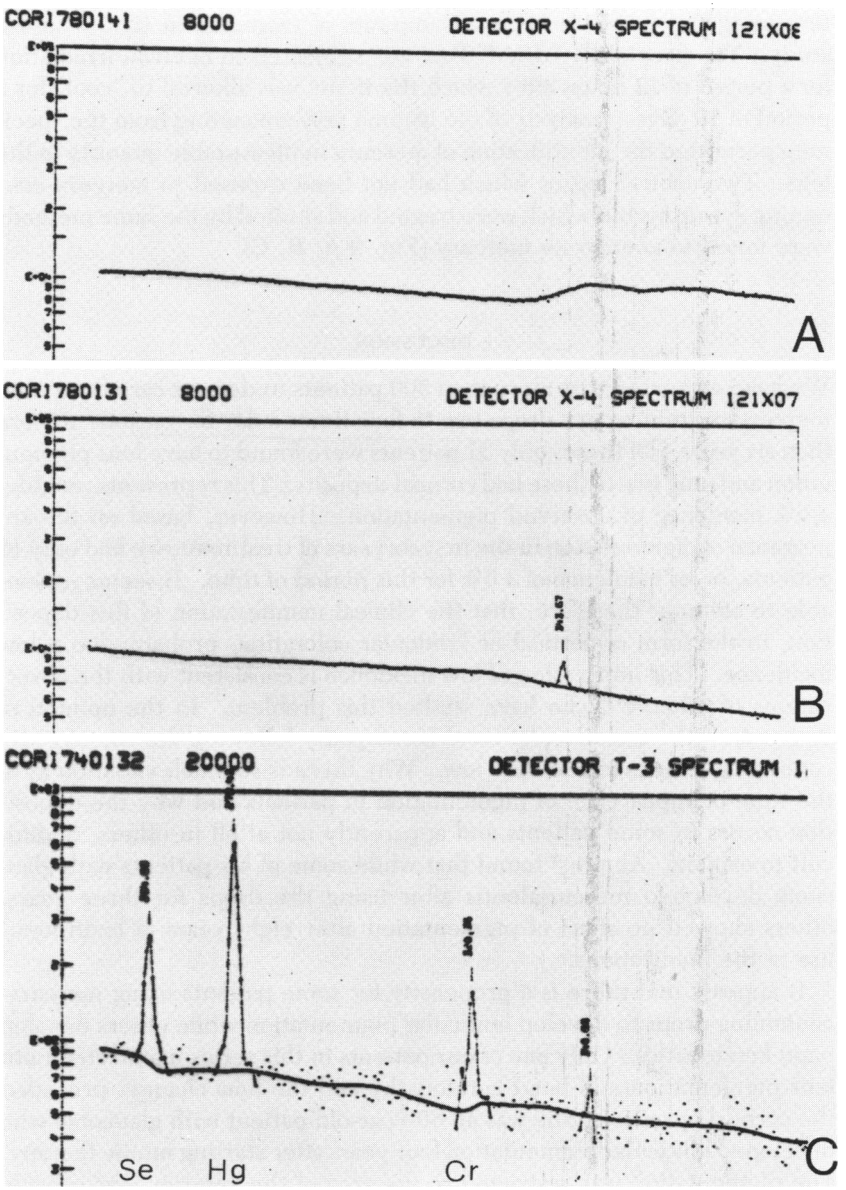

FIGURE 9

A: Control lens 1. Analysis spectrum shows mercury not to be present after neutron activation. B: Control lens 2. Analysis spectrum shows mercury not to be present after neutron activation. C: Analysis spectrum of left lens, Case 2 after neutron activation. Mercury (Hg) present 2.14 μg/g in specimen. Selenium (Se) and chromium (Cr) were also found.

termining the presence of small amounts of elements in tissues under study. The previously "dried" lens was subjected to neutron irradiation for a period of 12 hours after which the tissue was allowed to "cool" for a period of 10 days. Analysis of the gamma rays emanating from the specimen permitted the identification of mercury in measurable quantity in the lens. Two control lenses which had not been exposed to mercury-containing eye drops but which were treated and studied by the same methods were found to contain no mercury (Fig. 9 A, B, C).

DISCUSSION

We have estimated that more than 500 patients under our care have used mercury-containing eye drops two to four times a day for periods of more than six years. Of these, only 31 patients were found to have lens pigmentation and only two of these had corneal deposits. This represents roughly, a 6% incidence of observed pigmentation. However, based on the appearance of pigmentation in the first six years of treatment, we had only 18 patients, or an incidence of 3.6% for this period of time. It seems reasonable to assume, therefore, that the clinical manifestation of this deposition, in the form of corneal or lenticular coloration, probably has a low incidence. This impression of low incidence is consistent with the observations of others[3,12] who have studied this problem. In the opinion of Kennedy,[10] the incidence of band keratopathy following the use of PMN containing miotics is also very low. Why there is so much variation as to the time of appearence of pigmentation in patients and why the deposition occurs in some patients and apparently not at all in others, is difficult to explain. Abrams[9] found that while some of his patients with glaucoma developed mercurialentis after using the drops for three years, others showed no signs of pigmentation after eight years of continuous use of the medications.

It appears that there is a propensity for some patients using mercury-containing drops to develop lenticular pigmentation while others develop band keratopathy. Only one of our patients in this series manifested both lens pigmentation and band keratopathy and the lens changes preceded the corneal opacities. She was an 80-year-old patient with glaucoma who developed lenticular pigmentation four years after starting miotic therapy. The pigmentation was restricted to the area of the anterior lens capsule exposed by the miotic pupil. With the pupil dilated, and using the high magnification of the slit lamp, a dull brownish granular pigmentation of the central portion of the anterior capsule could be seen. The corneas were perfectly clear and pigmentation was not noted there. Three years

later, or seven years after the PMN containing miotic was started, she was found to have mild band keratopathy in each eye. In the right eye, nasally and temporally, were typical, grayish, ground-glass colored opacities beneath the epithelium. Each measured roughly 2-3 mm in diameter and was separated from the limbus by a clear zone of cornea. In the left eye, there was a similar opacity on the nasal side. During the next two years of observation, the corneal opacities enlarged somewhat, but the visual axis was never involved nor was there any discomfort attributable to these lesions.

Kennedy[10,11] reported the development of band keratopathy in 18 patients using a miotic containing PMN. Keratopathy developed in 16 of the 18 patients after they were on miotic therapy for 6 to 16 years while two showed it in less than one year's time. He did not mention the presence or absence of mercurialentis in this group of patients.

Burn[3] reported 57 patients with mercurialentis out of 70 workers from a thermometer factory. Of these, 6 also had band keratopathy and had been exposed to mercury for more than 17 years. Burn felt that the corneal changes result from exposure to mercury just as the lens changes do, but that they take much longer to develop.

The prolonged daily use of a mercurial ointment around the eyes has also been implicated in the production of mercurialentis. Abramowicz[13] reported the findings in a woman who had used a mercury ointment daily for blepharitis over a period of 41 years. The skin of the lids had assumed a bluish-grey color and in the bulbar conjunctiva, near the cornea were dark pigment granules. The peripheral portion of Descemet's membrane had a greenish or bluish-grey coloration and on the lens, in the pupillary area, was a dull granular, yellowish-brown deposition. Fischer[14] has also observed and recorded one case of mercurialentis which followed local applications of mercurial ointments to the lids over a long period.

Until recently, approximately 20% of all commercially prepared ophthalmic solutions were preserved with one of the following organic mercurials: phenylmercuric nitrate, phenylmercuric acetate and thimerosol.[15] The first of these, PMN, which probably was responsible for the band keratopathy reported by Kennedy[11] and for the lens pigmentation in our series, is no longer used to preserve pilocarpine solutions. However, PMN is still used as a preservative in a number of other ophthalmic preparations in common use. Phenylmercuric acetate is used as a preservative in three commercially available ophthalmic preparations but has been withdrawn from the epinephryl borate solution discussed in this paper. Of the mercurials, thimerosal is the most widely used preservative in opthalmic solutions and ointments. One popular form of artificial

tears uses this preservative, as do a variety of medications, including some antibiotics and a steroid suspension. In the years to come it will be of interest to see if patients who have been on medications containing thimerosal or phenylmercuric acetate, do develop corneal or lenticular pigmentation. Abrams, Davies, and Klein[16] described 21 patients with glaucoma who had used miotics preserved with thimerosal. After using these drops for two to four times daily for periods of four to ten years, none showed typical mercurialentis. However, the authors note that a very slight yellow tinge of the anterior lens capsule was seen. In our opinion, this might constitute a mercury related deposit. Comparing PMN and thimerosal, they claim that the latter is more soluble and therefore more stable chemically, and less likely to deposit out in the tissues. They attribute the ability of PMN to deposit readily in tissues to the fact that the PMN chemical formula is relatively unstable due to "the partly inorganic bonding of mercury," permitting metallic mercury to precipitate out of solution. These factors need further elucidation. It would be helpful to know how and in what form the mercurials are transferred into the eye and in which chemical forms they are deposited on the lens.

The mercurialentis which develops in industrial workers, following prolonged contact with metallic mercury, seems to differ somewhat from that in patients who have acquired their pigmentation by the medicamentous route. In our patients and in those described by Abrams,[9] the pigmentation seems to be localized in the pupillary area. Our observations indicate that with the pupil dilated, the anterior lens capsule is clear peripheral to the original pupillary zone, and is devoid of pigment. In industrial workers,[1,3,4,6,7,8] most of the anterior lens capsule is said to be pigmented, though most observers note that the pigmentation in the pupil is most intense. It is possible that in industry, the exposure of the eyes to high concentrations of mercury (mercury vapor and metallic mercury) permits more of the metal to gain entrance to the interior of the eye for a more widespread deposition than is possible when a dilute solution of mercury is dropped into the conjunctival sac a few times a day. Because the anterior capsule centrally is not covered by iris, it would logically be the site of heavier deposition in either case. Abrams notes[9] that in some of his patients who had had prior iridectomies, he occasionally found mercurial pigments deposited on the exposed lens capsule, noting that the deposition was not restricted to the pupillary area as it is in eyes that have not had surgery.

Several observers have assumed that the pigmentation of the anterior capsule of the lens represents deposits of mercury or mercurial compounds. Others have inferred that these deposits are melanin combined

with some compound of mercury. The pigmentation seen clinically appears to become more prominent with time, suggesting that the change of color is the result of progressive deposition. With light and electron microscopic studies, we find densly pigmented particles deposited on the lens capsule which resemble melanin. Within the capsule, the deposits are mainly dust-like, and some of these particles have penetrated the capsule and have deposited within the cytoplasm of subcapsular epithelial cells. By these methods it is not possible to determine if mercury in any form is a constituent of these deposits.

Atkinson and von Sallmann showed trace amounts of mercury to be present in two lenses by histochemical and spectographic methods.[2] The techniques used by them are not as sensitive as those currently available. We attempted to identify mercury or its compound within the lenticular deposits by using the technique of "electron microbeam excitation of characteristic X-rays", a combination of the scanning electron microscope and energy dispersive X-rays with the electron microprobe. With this method it is possible to identify relatively small amounts of elements and to localize them, such as in the pigmented area of the lens capsule. As previously mentioned, the response for mercury was minimal, suggesting that mercury was a very dilute constituent of the material in the pigmented area.

The technique of "X-ray fluorescence" was used on a whole lens (left lens of Case 2) after it was prepared by critical point drying. The results of this method were equivocal, suggesting that the mercury content of the lens was not sufficient to be identified by this technique.

In 1970, Abrams and Majzoub[12] were able to identify the presence of mercury in the lens of a patient with mercurialentis by using the technique of "activation analysis." They demonstrated 13.5 times the amount of mercury in a lens with mercurialentis than was present in two control lenses. The actual mercury content of the analysed lens was 1.08 μg/gram. This is the most sensitive method currently available to measure small or trace quantities of elements in material. The left lens of Case 2 was subjected to "neutron activation," a method which is similar to the "activation analysis" utilized by Abrams and Majzoub. Mercury in the amount of 2.14 μg/gram was found in our specimen. Two control lenses contained no measurable mercury.

The discreptancy between the ready visibility of the lenticular pigmentation observed at the slit lamp and the demonstration of pigmented material on and in the lens capsule by light and electron microscopy, as opposed to the relatively minute amounts of mercury identified by the techniques mentioned above, suggests that the pigment observed clinically is

primarily of melanin derivation in which there may be minute amounts of mercury.

SUMMARY

Thirty-one patients who used eye drops containing the preservative, phenylmercuric nitrate for from 3 to 15 years, developed a brownish pigmentation of the anterior capsule of the lens in the pupillary area. Light and electron microscopic studies on two lenses demonstrated deposits of dense particulate material resembling melanin pigment on and in the anterior capsule of the lens in the area of the pupil. Special studies, including electron microprobe analysis and neutron activation analysis established the presence of mercury in a lens with mercurialentis. No mercury was found in two lenses used as controls.

ACKNOWLEDGEMENTS

Special thanks are due to Dr. Wesley Estill of the Sandia Corp., Livermore, CA, for his advice and help with the electron microprobe studies. Dr. Rolf Woldseth of the Kevex Corp., Burlingame, CA, was most helpful with advice and with the X-ray fluorescence studies. Dr. John Long of the Department of Anatomy, University of California, San Francisco, CA, kindly prepared the lenses by critical point drying. Dr. David Camp and Mr. Robert Heft of the Lawrence Livermore Laboratories, Livermore, CA, very graciously carried out the neutron activation studies. Mr. Fujio Jimbo of JEOL, Inc., Burlingame, CA, was most helpful with some of the electron microprobe studies.

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DISCUSSION

Dr Irving H. Leopold. The history of mercury poisoning is much like that of lead poisoning in that what used to be a rare occupational hazard has today become a serious problem for entire populations.

The general principle that wholesale pollution of the biosphere by numerous products and byproducts of our technology has placed great numbers of people at risk who may have no occupational relationship to all of these poisons.

As an occupational hazard, mercury poisoning affected chiefly miners and those in the felt-hat industry. Metallic mercury vapor was responsible. The effects were mostly in the kidneys and nervous system—the term "mad as a hatter" came from this—presumably following oxidation of mercuric ion in the body.

Mass poisoning occurred with the introduction of alkyl mercury compounds in certain industrial processes and as fungicides. As with chorinated hydrocarbon pesticides, the magnification of organic mercurial concentrations through the food chain was responsible. The process is exemplified by the remarkable story of Minamata's disease (*World Neurology* 1:370, 1960).

In 1956, a new factory on the shores of Minamata Bay in Japan began producing vinyl chloride and acetaldehyde. Wastes containing methyl mercury were dumped into a nearby creek. Within a year a strange illness appeared in the families of fishermen along the bay. Neurologic symptoms predominated, beginning with memory loss, parasthesias, ataxia, narrowing of the visual field, progressing to emotional instability and loss of muscle coordination. Small children and newborns were affected most severely.

The astute observation that cats in the affected households suffered from the same symptoms eventually led to the discovery of the cause and the whole chain of events from factory to man was worked out. High concentrations of methyl mercury entered the bay, were taken up and stored by lower organisms, which were eaten by shell fish and the shell fish were eaten eventually by people and cats.

Metallo-organic compounds pass the blood-brain barrier more readily than free metal ions. Therefore, methyl mercury salts are more toxic than mercuric salts to the nervous system. As soon as the factory waste was diverted from Minamata Bay the epidemic subsided.

Although the dangers of organic mercurials have been publicized, poisonings have continued to occur. In New Mexico, grain intended for seed purposes and treated with a fundicide cyanomethylmercury guanidine was fed to hogs. Meat of these animals eaten three months later produced ataxia, agitation and visual im-

pairment. This occurred in 1971 (*Science* 172:65, 1971). In 1972, poisoning from ingestion of mercury-treated seed grain occurred on a mass scale in Iraq (*Science* 181:230, 1973). Epidemics such as these brings up the question of the extent that the environment air, water, and food supply may be polluted by mercury.

Drs Garron, Wood, Spencer, and Hayes have concisely confirmed the observation of others that the eye may show depositions of mercury in the cornea and the lens. They have added the possibility of involvement of the trabecular meshwork and of the optic nerve head following topical application of ophthalmic preparations. Although the materials had been identified previously in the lens by histochemical, spectrographic, and activation analyses this is the first report of attempted identification using an electron probe.

It should be noted that there is a noninvasive method using X-ray excitation spectrometry for quantitation of trace metals in the eye, such as that used by Belkin and co-workers to follow the effects of therapy on corneal copper in hepatolenticular degeneration. Perhaps this technique could be developed for other trace metals such as iron, nickel, zinc and mercury (*Lancet* i:391, 1976).

It is well established that of the preservatives used in ophthalmic solutions phenylmercuric nitrate and acetate have a much greater chance of inducing this change than thimerosal. It is probably the poor solubility of phenylmercuric nitrate and acetrate that accounts for this striking difference. There appears to be very little risk with the soluble thimerosal.

The distribution of the deposits on the exposed pupillary zone and iridectomized area of the lens probably indicates precipitation on the iris as well. Some of this may be removed from the iris by the circulation. The mercury may be there as well, but not visualized because of the iris pigmentation.

Why do so few show this deposition after years of use of the phenylmercuric preservatives? Could this be related to the variable extent that each individual is exposed to mercury in his or her own environment? Dentists have developed mercurialentis after using amalgams for dental work. Could the number of such amalgam fillings be important? Could the dietary habits be important? What has been the environmental exposure to mercury of those with mercurialentis as opposed to those without? Could there be some differences in the contents of the aqueous humor of those with deposits and those without? The same question would apply to the characteristics of the tear film in those two groups of patients—those with corneal changes and the ones without.

High concentrations of mercury have been found in the fish of Lake Michigan. What about the San Francisco Bay area? Latex paints often contain mercury compounds as mold retardants. Enclosed environments painted with this could lead to high vapor content, similiarly in dental offices and laboratories where amalgams are used.

Organic mercurials are more potent mutagens, (that is they may produce chromosomal breakage) than colchicine which is thought to be very active in this respect. Mercurials are teratogenic at concentrations lower than those which cause illness in the mother. Perhaps it will become necessary to reduce the total environmental burden of mercury.

Fortunately, the mercury deposits in the eye do not seem to bother visual function. However, it would be interesting to see if any of these deposits could be lessened or removed by therapy with mercury chelating agents such as dimercaprol (BAL).

Mercurialentis does not cause any damage to sight but band keratopathy may do so. One would certainly be justified in trying chelation therapy on mercury-induced band keratopathy.

It is somewhat overwhelming to realize that in 1976, in the Bicentenial year, we are discussing the toxicity of mercury. This was a favorite topic in the writings of Hippocrates, Pliny, Galen, and others. The possible effects of mercury vapor as an industrial hazard appeared in the treatise by Orik Ellemborg written in 1473—500 years ago (*Ann Med History* 8:27, 1936).

This has been a very stimulating paper and I have enjoyed the opportunity of studying it prior to the meeting.

DR WILLIAM RICHARD GREEN. Mr President, Mr Secretary, ladies and gentlemen. Recently we've had the opportunity to study eyes obtained postmortem from two patients in whom chronic mercury poisoning occurred as the result of chronic use of a mercuric-chloride-containing cathartic. We found the deposition of mercury in the cornea to be somewhat similar to the distribution seen in the Kaiser-Fleischer ring. We did not find any mercury in the lens capsule. Analysis of the various body tissues for mercury disclosed the greatest concentrations in the choroid plexus, the kidney, and the cornea. These corneal deposits had not been observed clinically.

DR HAROLD GIFFORD. During the last year I have seen seven patients who had a discoloration of the lens capsule. I found that five of the first six were using pilocarpine. The sixth patient is a dentist who has been handling an amalgam of mercury and silver for thirty years. The seventh patient was seen just before leaving for this meeting, and was also using pilocarpine for glaucoma.

The first five examples were found because I was looking closely at the lens capsule for another reason. I simply listed these as having a pink capsule. When I looked at the records of these five patients, four of the five had glaucoma. The sixth one was found because she had the corneal opacities (unusual band keratopathy) caused by the mercury perservative used in some pilocarpine solutions. Her record showed that the pink discoloration was seen in her capsules after the cornea was cleared by chelation.

The color is seen best with the slit lamp beam at a twenty to thirty-five degree angle focused sharply on the surface of the capsule and about one to two millameters wide. It is very faint but it is unmistakable after you have once seen this effect. It can be seen with the light coming from either side and does not have an iridescence.

Case 1. Male. Age 76. Patient using pilocarpine 1% for ten years. Tension has been fairly well controlled. Vision was 20/30 right and 20/60 left with tension 17 both eyes. Eppy ½% had been added to regimen for the last year. Slit lamp

examination showed a convex curve to the temporal side, almost like a rainbow, brought out best with illumination from the nasal side also present the other way. This is a central area 2×3 mm of brownish red staining in the anterior capsule centered just above and nasally. The left eye showed a similar change in the capsule.

Case 2. Male. Age 70. Glaucoma ten years. Using 5% pilocarpine every three hours. 2% Glaucon once daily. Vision both eyes 20/50. Only a lower temporal field remaining. Tension OD 22, OS 28. Pupils were small. Slit lamp OD: Little brownish discoloration of the capsule maybe reflected light from pigment of the small pupil. OS: similar with light from the temporal side. Nucleus a little dense. Trephine operation June 1975. Pink discoloration present previous to the trephine. Tension was OD 22, OS 32. Pink discoloration of the central pupillary area, limited to the capsule.

Case 3. Age 66. Glaucoma for thirteen years. Using pilocarpine three times a day both eyes. Vision 20/200 right, 10/200 left. Retina showed cystic macular degeneration in both eyes. Tension 19 Schiøtz. The left eye central lens capsule had a pinkish discoloration. There also appeared to be a reddish tinge to Descemet's membrane which appeared to be optical. Later the Descemet's membrane showed no color but the color definitely present in the lens.

Case 4. Female. Age 63. Patient has had glaucoma for the past seven years. Was using 2% pilocarpine then, was on 4% pilocarpine and is now on 6% pilocarpine. These are prescriptions given by three different doctors. The tension was right eye 25, the left 23. Vision OD 20/20, OS 20/20. Slit lamp examination showed a little pinkish look to the capsule. Slightly iridescent sheen also a pink look to the temporal side with the extra bright light, there it has a fine granular appearance.

Case 5. Female. Age 76. Patient has had glaucoma for many years. Using 4% pilocarpine. She developed the typical corneal opacities with mercurial deposits from the use of pilocarpine. These were chelated successfully. Following the chelation, the capsules were noted to show this reddish brown discoloration seen in the other patients. Discoloration is limited to the central area and is a little less in the left eye.

Case 6. Male. Age 50. Has little reddish tinge to capsule. No granular deposits. Descemet's membrane maybe a little exaggerated. He gives a history of handling mercury and silver amalgam going back thirty years. Originally mercury and the silver were mixed and pressed through a squeeze cloth to squeeze out the extra mercury. Now it is done by having two metals in a capsule. The partition is ruptured and the capsule is shaken mechanically to produce the amalgam. Patient has never used any eye drops.

Case 7. Female. Age 61. Patient has been using pilocarpine 1%, 1 drop every 4 hours for 16 years and Eppy 1 drop daily for 8 years. Both lens capsules show the pinkish discoloration.

I was suprised to find that Walsh's textbook of Neurology first edition 1947, had a reference to this condition in his discussion of mercury poisoning (*Arch Ophthalmol* 30:287, 1943). This was a paper presented by Dr Walter Atkinson to the Section of

Ophthalmology of the N.Y. Academy of Medicine in 1943 (34 years ago). He found this condition in 37 of 70 individuals in contact with mercury for a period of year. Fourteen of these had symptoms of mercurialism (tremors, inattention, excitement, stomatitis, gastrointestinal and renal damage). His description of this condition is very good. "It is a rather homogeneous reflex seen well with slit lamp containing a low power objective. It varies from a light brownish gray to a deep rose-brown, and the color is deeper in the pupillary area." Dr Maynard Wheeler congratulated Dr Atkinson for finding something completely new in ophthalmology.

I feel certain that many more examples will be found among dentists, dental assistants and patients using pilocarpine. It is amazing to me that this has been seen so infrequently. Dr Garron should be congratulated for bringing this to our attention, and proving so beautifully that it is a deposit of mercury in the lens capsule.

Dr Robert Kennedy. To me this is a very exciting paper and one that has been very throughly researched with the information on the lens well documented. Doctor Atkinson, also from Upstate New York, presented this paper on the evaluation of a lens in 1946, which was the year I first met him. He had already presented the clinical observations on mercurialentis some four years before.

We had a large thermometer manufacturing industry in Rochester. Upon returning to Rochester I happened to see many patients from that company and soon noticed an occasional lens discoloration as he had described. Being aware of the phenomenon, I next noted it in some dentists and thought this might be an original observation until I reviewed the literature and found described in the 1949 American Dental Journal "A newly observed ophthalmic occupational hazard in dentistry."

The next occasion was to see these changes in patients with glaucoma in the early and middle 1960's. At the same time it was noted that there were also occasional corneal opacities. These were described in papers before this Society in 1971 and in 1974, and represented calcium deposition in the corner. These slides show the characteristic lesions and are slides from these papers.

While we were examining these patients for more examples of what we called "atypical band keratopathy" we began to notice a correlation of the lens changes of discoloration of mercurialentis with those having the corneal changes. This was so characteristic that we were able to designate the manufacturer of the pilocarpine being used by these patients. At the time with some twelve companies making pilocarpine, only one was using phenylmercuric nitrate as a preservative. By the time some 50 cases had been observed you could practically tell from the corneal changes, or more particularly the mercurialents changes, that they were using the pilocarpine of the one company with the mercurial preservative.

It is of clinical interest and a real credit to the company involved that after talking this problem over with them in March 1973, in about six weeks all of the mercurial preservative had been removed from their pilocarpine.

In our 1974 publication, we did remark about our lens evaluation for mercury. I have to take my hat off to Dr Lee Garron and his group for their detailed study. We could not get cooperation at our medical school for adequate lens evaluation which was done more accurately by industry. To my knowledge, the only lenses which have been evaluated are those of Atkinson in 1946, Abrams in 1948, our three mentioned in 1974, and the two by Dr Garron for a total of seven.

We determined quantitatively the amount of mercury by atomic absorption and neutron activation techniques. We evaluated three lenses of patients who had used pilocarpine containing the phenylmercuric nitrate, two lenses of patients using pilocarpine without the mercurial preservative, and two normal lenses, along with some gelatin controls impregnated with a measured amount of mercury. The three lenses of the patients using the pilocarpine with phenylmercuric nitrate showed an increase of 8 to 10 times the amount of mercury as the other lenses. We did not have the facilities to go into the detailed evaluation that Dr Garron performed.

I think it is of interest as already pointed out to realize that there is a very extensive deposition on the posterior cornea in these patients. This is readily seen in an occasional dentist, usually the older men who mix their amalgam by hand. This method is readily being replaced by turning the dial and pushing the button for their desired mixture.

I feel that Dr Garron and his group have performed a most thorough investigation.

Thank you.

DR CLEMENT MCCULLOCH. In the northwest corner of Ontario, near Souix Lookout, there is a lake into which a paper company has been dumping mercury. A lot of this material has accumulated at the bottom of the lake and the river system that flows from it. This material lies there with the water flowing over its surface, and, in all probability, will remain there for years to come. The fish are contaminated by it and Indians in that district have peculiar symptoms which might be due to Minamata disease.

Dr J.S. Crawford was a member of the team that went to investigate this Ontario site, and also similarly affected areas in Japan and Iraq. The Canadian government had sent some wheat to Iraq for seed purposes. To keep it well perserved, as it was not going to be used for human consumption, it was treated with mercury to prevent fungus. The bags were carefully marked "poison, not to be eaten". However, when the shipment reached Iraq, the people did eat it, and there were many cases of mercury poisoning in that country.

Dr Crawford did not find a lot of pigmentation in the lens even though he knew of the possibility and was carefully looking for it. It may be that under certain circumstances the mercury will stain the lens and in other circumstances it will not, as Doctor Leopold suggested.

One interesting thing is that mercury seems to be deposited in great quantity in the calcarine fissure, which may have a relation to the restricted fields which these patients showed.

We are now wondering whether we should go to the tremendous expense of dredging out this whole lake and river system below the paper mill or just leave it.

Dr Levon K. Garron. I would like to thank all of the discussants for their kind remarks and for adding so much to our paper. Doctor Leopold's discussion of the toxic effects of mercury via the gastrointestinal tract was most pertinent. The acute mercurialism which results from the intake of relatively large amounts of mercury in a short space of time is a devasting disease. It often leads to death and contrasts with the disorders which result from the absorption of small quantities of mercury over long periods of time. Workers involved in the manufacture of batteries and thermometers and in other industries where there is prolonged exposure to mercury, often develop signs of chronic mercurialism. In these individuals the absorption is through the skin or mucous membrane into the blood stream, followed by deposition of mercury compounds in various tissues of the body. Where lenticular pigmentation is also observed, it is persumed that metallic mercury, mercury vapor or some compound of mercury has entered the anterior chamber directly through the conjunctiva or cornea, and not via the blood stream. Many observers have noted that pigmentation of the lens precedes the signs and symptoms of systemic mercurialism, reinforcing the opinion that the ocular findings follow a direct passage of the mercury into the eye and are probably unrelated to mercury absorbed through the gastrointestinal tract or through the skin.

In our patients, a mercurial preservative was instilled into the eyes for a prolonged period. Under high magnification, we were able to see fine dust-like particles in the tissues of the limbus and these we have interpreted to be related to this preservative. As yet, we do not know if the phenylmercuric nitrate passes into the anterior chamber as such or if it is converted into some other mercury compound on the way.

The question of the nature of the lenticular pigmentation is of considerable interest. With magnification, the deposition closely resembles melanin. Presumably, the mercury in the circulating aqueous is toxic to pigmented cells, as in the iris, resulting in a release of melanin debris. The deposition of the pigment on the lens is very likely fortuitous, since the exposed lens capsule seems to be mainly favored. In all of our patients the iris angle also seemed to have more than the usual degree of pigmentation. We are in the process of determining if this pigment material is of melanin derivation. Mercury was found to be present in a measurable amount in the whole lens examined. However, we are not able to determine if the mercury is distributed generally throughout the lens or if it is localized strictly near the pupillary lens capsule, where there was clinically observable pigmentation. Our tests with the electron probe indicated the presence of only trace amounts of mercury in the pupillary area, where pigment is deposited. Therefore, while mercury is identified in these lenses, it is unlikely that it is localized only where we find pigmentation.

Dr Kennedy, I am happy that you were able to establish the presence of mercury in your patients and that you were able to quantitate it. Doctor Gifford, you were kind to collect and to report the findings in your patients. At

least, you have added further evidence that this condition exists and that it may follow the use of eye drops containing a mercurial preservative. Many thanks. I hope I have answered all of the questions asked.

Before closing I would like to tell the story of the thermometer factory worker who consulted his physician and stated that he was afraid he had mercury poisoning because he was much taller in the heat of summer than he was in the cold of winter.